REMARKS

Claims 1-4, 6-9, 11, 14, and 15 are pending in this application. Claims 1-4, 6-9, and 11 stand rejected. Claims 12, 14, and 15 have been withdrawn from consideration as being drawn to the non-elected invention. None of the claims stands objected to.

In view of the following amendment and response, the Applicants believe the claims presented herein are allowable. Reconsideration is respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-4, 6-9, and 11 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Kuo, *et al.* in view of Masure *et al.*

First and most importantly, it is respectfully submitted that in order to establish a *prima facie* case of obviousness, the PTO must satisfy certain requirements. Among them, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See Karsten Mfg. Corp. v. Cleveland Gulf Co., 242 F. 3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001). Thus there must be a positive teaching in the prior art to suggest or provide incentive to motivate a skilled artisan to combine references.

However, the Examiner at the end of the Office Action dated March 9, 2004 (page 5, last two lines) concluded:

> ***There is nothing on the record to show that combination of teaching would not suggest the claimed invention.***

It is respectfully submitted that the Examiner is clearly relying on an erroneous standard of obviousness because the Applicants do not have the initial burden of providing with anything ***to show that combination of teaching would not suggest the claimed invention*** (*i.e.* proving the negative). Rather, it is PTO's duty to come forth with the record that suggests the combination would work.

The Examiner states on page 4 of the Office Action that there is no limitation or requirement in the claims that the composition comprises "at least one unconjugated *Streptococcus pneumoniae* protein antigen." For the purpose of clarification, amendment is made to the claim 1 to add the wording "unconjugated." In all the Examples in the specification when *Streptococococcus pneumoniae* protein antigen is employed as a second component, it is always used as an unconjugated form (namely see Examples 4B, 4C and 5); thus, the amendment does not add new matter. The amendment is made only to ensure that both the Examiner and the Applicants have the same understanding of the claims.

The Examiner states

> *It would be prima facie obvious at the time the invention was made to add the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pnueumolysin conjugate vaccines as taught by Kuo et al because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection, including but no [sic] limited to antibiotics, soluble carbohydrate inhibitors of bacterial adhesion, other small molecule inhibitors of bacterial adhesion, inhibitors of bacterial metabolism, transport or transformation, stimulators of bacterial lysis or antibacterial antibodies or vaccines directed at other bacterial antigens (column 30, lines 34-42). It would be expected barring evidence to the contrary, that the addition of the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al would be effective in treating Streptococcus pneumoniae infections. (Emphasis added).*

Kuo *et al.* discuss a vaccine comprising pneumococcal polysaccharides conjugated to pneumolysin. There is no mention of any need to further supplement this vaccine with other antigens to improve its efficacy against pneumococcal disease. It does disclose that the composition may be formulated with one of many adjuvants. However, rather than just Th1 adjuvants being mentioned, many Th2 type adjuvants are also suggested (such as aluminium hydroxide and aluminium phosphate). There is therefore no clear direction to using a Th1 adjuvant in this composition.

Masure *et al.* suggest using Cbps in a pneumococcal vaccine. The Examiner places great stock in the passage on column 30 lines 34-42 where Masure *et al.* suggest that the

compositions of the invention may be administered "with one or more pharmaceutical compositions used for treating bacterial infection, including but not limited to (1) antibiotics, (2) soluble carbohydrate inhibitors of bacterial adhesion, (3) other small molecule inhibitors of bacterial adhesion, (4) inhibitors of bacterial metabolism, transport or transformation, (5) stimulators of bacterial lysis, or (6) antibacterial antibodies or vaccines directed at other bacterial antigens." Note that Masure *et al.* only mention this as a possibility among many wide choices, and do not specify adding other pneumococcal vaccines to the composition - merely suggesting other antibacterial vaccines. In fact this passage could be interpreted as adding antigens from bacteria other than pneumococcus to the vaccines of the invention. Contrary to what Examiner alleges, this passage does not provide any motivation to combine the Cbp compositions with Streptococcus pneumococcal antigens.

It should therefore be emphasized the composition of the present invention can only be achieved starting with Masure *et al.* that (step 1) a skilled person would have to be motivated to select "antibacterial vaccines" from wide choice of possible addends (1)-(6) of column 30, lines 34-42, and (step 2) subsequently choosing Streptococcus pneumococcus antigens from all "antibacterial vaccines." Even *arguendo* if there was such a motivation, the skilled person would then have (step 3) to decide to add pneumococcal polysaccharide conjugate antigens, and furthermore (step 4) be motivated to select a Th1 adjuvant from the list of Th1 and Th2 adjuvants that Kuo *et al.* discloses.

It is our submission therefore that although a skilled person could have carried out these four quantum leaps, they would not have done with any reasonable expectation of obtaining the advantages set out in the present invention. To suggest otherwise would involve a hindsight analysis of the prior art using the teaching of the present invention - which of course is an impermissible approach to the analysis of obviousness.

Lines 6-13 of page 9 of the present application states:

> Surprisingly, the present inventors have found that by simultaneously stimulating the cell mediated branch of the immune system (for instance T-cell meditated immunity) in addition to the humoral branch of the immune system (B-cell mediated), a synergy (or cooperation) results which is capable of enhancing the clearance of pneumococci from the host. This is a discovery which will aid the prevention (or treatment) of pneumococcal infection in general, but will be

particularly important for the prevention (or treatment) of pneumonia in the elderly where polysaccharide based vaccines do not show efficacy.

The present inventors have found that both arms of the immune system may synergize in this way if a pneumococcal polysaccharide (preferably conjugated) is administered with a pneumococcal protein (preferably a protein expressed on the surface of pneumococci, or secreted or released, which can be processed and presented in the context of Class II and MHC class I on the surface of infected mammalian cells). Although a pneumococcal protein can trigger cell mediated immunity by itself, the inventors have also found that the presence of a Th1 inducing adjuvant in the vaccine formulation helps this arm of the immune system, and surprisingly further enhances the synergy between both arms of the immune system." This is further supported by the Examples (see for instance Examples 4 and 5; more particularly see e.g. Figure 1C, page 50, lines 10-16; page 53, lines 1-3; and page 55, lines 15-18 of the specification) where this cooperation is shown for a particular combination of antigens.

Neither Kuo *et al.* nor Masure *et al.* discuss such advantages of combining pneumococcal polysaccharide conjugates with CbpA and Th1 adjuvant to achieve the above advantages. No motivation is provided from anywhere to combine these antigens together. It seems incredulous that a skilled person would make the leaps/selections discussed above to arrive at the present invention with no motivation. The present invention is therefore unobvious over the cited prior art.

Minor amendments were made to claims 2, 3, 4, 6, and 9 to clarify the antecedent basis. Also dependency to claim 11 has been increased by making it dependant to any one of claims 1-9. The Applicants respectfully submit that, in view of the forgoing remarks and the claims as amended, the Applicants have overcome the rejection of Claims 1-4, 6-9, and 11 under 35 U.S.C. § 103(a). Accordingly, the Applicants respectfully request reconsideration and withdrawal of these rejections.

The Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly,

favorable reconsideration and allowance of the pending claims is earnestly solicited. If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,

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